SUPPLEMENTARY INFORMATION
for

Secondary metabolites from Hypocrealean entomopathogenic fungi: Genomics as a tool to elucidate the encoded parvome

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HEF genomes considered for the analysis described in Part 4 and Figure 1 were:

Clavicipitaceae: *Hypocrella siamensis* MTCC 10142;[1] *Metarhizium acridum* CQMa 102;[2] *Metarhizium album* ARSEF 1941;[3] *Metarhizium anisopliae* E6;[3, 4] *Metarhizium brunneum* ARSEF 3297;[3] *Metarhizium guizhouense* ARSEF 977;[3] *Metarhizium majus* ARSEF 297;[3] *Metarhizium rileyi* RCEF 4871;[5, 6] *Metarhizium robertsii* ARSEF 23;[2, 3] *Moelleriella libera* RCEF 2490.[6]

Cordycipitaceae: *Beauveria bassiana* ARSEF 2860;[7] *Beauveria brongniartii* RCEF 3172;[6] *Beauveria pseudobassiana* KACC 47484;[8] *Beauveria rudraprayagi* MTCC 8017; *Cordyceps* (formerly *Isaria*) *fumosorosea* ARSEF 2679;[6] *Cordyceps cicadae* CC02;[9] *Cordyceps confragosa* RCEF 1005;[6] *Cordyceps farinosa* KACC 47486;[8] *Cordyceps militaris* CM01;[10] *Cordyceps pruinosa* KACC 44470;[8] *Cordyceps tenuipes* KACC 47485;[8] *Cordyceps javanica* IJ2G;[11] *Lecanicillium psalliotae* HWLR35;[12] *Lecanicillium* sp. LEC01;[13] *Lecanicillium* sp. MT-2017a AZ2; "*Paecilomyces hepiali*" FENG;[14] *Torrubiella hemipterigena* (formerly *Verticillium hemipterigenum*) BCC 1449.[15]

Ophiocordycipicaeae: *Cordyceps* sp. RAO-2017 strain 1346; *Hirsutella thompsonii* MTCC6686;[16, 17] *Ophiocordyceps australis* Map64;[18] *Ophiocordyceps* sp. 'camponoti-leonardi' BCC 80369;[19] *Ophiocordyceps camponoti-rufipedis* Map16;[18] *Ophiocordyceps* sp. 'camponoti-saundersi' BCC 79314;[19] *Ophiocordyceps polyrhachis-furcata* BCC 54312;[20] *Ophiocordyceps sinensis* ZJB12195;[21] *Ophiocordyceps unilateralis* SC16a;[18, 22] *Tolypocladium inflatum* CBS 567.84;[23] *Tolypocladium paradoxum* NRBC 100945.[24]

Hypocreales incertae sedis, sister to Ophiocordycipitaceae: *Trichothecium ovalisporum* DAOM 186447;[25] *Trichothecium roseum* DAOM 195227.[25]

Table S1. Genomics-based prediction of the parvome of *Metarhizium* spp. whose genome sequences have been analyzed[26 27 28 29 30]

Core gene group[1]	**Secondary metabolite product**[2]	**Notes**[3]
M-NRPS11	Predicted cyclic tetrapeptides similar to HC-toxin (**44**) or apicidin (**45**)	Present only in *M. majus*.[27]
M-NRPS12	Predicted ferrichrome siderophores similar to malinochrome (**46**)	Present only in *M. album* and *M. majus*.[27]
M-NRPS15 + M-NRPS16 + M-TER30	Predicted ergot alkaloids similar to ergonovine (**47**)[31]	Absent from *M. majus*.[27]
M-NRPS17 (MrSidC in *M. robertsii*; MaNRPS9 in *M. anisopliae* E6)	Ferricrocin (**14**)	Present in all sequenced *Metarhizium* spp.[27] Ferricrocin (**14**) was isolated from *M. robertsii* as a product of the MrSidC BGC whose disruption reduces but does not eliminate virulence.[32] Induced in *M. anisopliae* under conditions mimicking early infection.[26]
M-NRPS18 (MrSidD in *M. robertsii*; MaNRPS8 in *M. anisopliae* E6)	Coprogen siderophores such as metachelin A (**13**)	Missing from *M. album.*[27] Metachelin (**13**) was isolated from *M. robertsii* as a product of the MrSidD BGC whose disruption does not affect virulence.[32] Repressed in *M. anisopliae* under conditions mimicking early infection.[26]
M-NRPS19 (MaNRPS1 in *M. anisopliae* E6)	Destruxin A (**48**) and its congeners	Absent from host specialists.[27] Destruxins were isolated from *M. robertsii* as the products of the DTX BGC whose disruption slightly reduces virulence.[33, 34] Induced in *M. anisopliae* under conditions mimicking early infection and repressed in those for late infection.[26]

M-NRPS20 (MaNPS1 in *M. robertsii* ARSEF 2575; MaNRPS2 in *M. anisopliae* E6)	Serinocyclin A (**49**) and its congeners	Present in all sequenced *Metarhizium* spp.[27] Serinocyclins were isolated from *M. robertsii* as the products of the MaNPS1 BGC whose disruption does not affect virulence.[35] Repressed in *M. anisopliae* under conditions mimicking late infection.[26]
M-NRPS23 + M-TER27	Predicted prenylated epipolythiodiketopiperazine-type dipeptides similar to gliotoxin (**50**)	Absent from host specialists.[27]
M-NRPS24	Predicted epipolythiodiketopiperazine-type dipeptides similar to gliotoxin (**50**)	Only present in *M. guizhouense* and *M. robertsii*.[27]
M-NRPS25	Predicted epipolythiodiketopiperazine-type dipeptides similar to gliotoxin (**50**)	Absent from *M. album*, *M. majus* and *M. robertsii*.[27]
M-NRPS26	Predicted epipolythiodiketopiperazine-type dipeptides similar to gliotoxin (**50**)	Only present in host generalists.[27]
M-NRPS27 + M-PKS4	Predicted ochratoxin A (**51**)-type compounds[36]	M-NRPS27 members are only present in *M. brunneum* and *M. robertsii*.[27]
M-NRPS(PerA)*	Pyrrolopyrazines derived from peramine (**35**)[29]	Only present in *M. majus* ARSEF 297.[3, 29] The *M. majus* PerA orthologue from *M. rileyi* RCEF 4871 yielded peramine upon heterologous expression.[29] PerA is part of the PPZ BGC.[29]
M-NPL4	Predicted terrequinone (**52**) or microperfuranone (**53**)-like compounds	Only present in host generalists.[27]

M-NPL5 (MaOTHER12 in *M. anisopliae* E6)	Predicted terrequinone (**52**) or microperfuranone (**53**)-like compounds	Absent from host specialists.[27] Induced in *M. anisopliae* under conditions mimicking early infection but repressed under those for late infection.[26]
M-NPL6	Predicted terrequinone (**52**) or microperfuranone (**53**)-like compounds	Only present in host generalists.[27]
M-NPL8	l-α-aminoadipate-6-semialdehyde	Present in all sequenced *Metarhizium* spp.[27] Involved in lysine biosynthesis as a part of primary metabolism.[37]
M-PKS1 + M-PKS25	Predicted benzenediol lactone-type macrolides similar to monocillin II (**54**)[38]	Missing only from *M. acridum*.[27]
M-PKS7 + M-PKS22	Predicted asperfuranone (**55**)-like azaphilones[39]	Present only in *M. acridum*.[27]
M-PKS8 + M-PKS23	Predicted acyl orsellinaldehyde (**56**)-type compounds[40]	Absent from host specialists.[27]
M-PKS9C + M-NRPS3C	Predicted phomenoic acid[41] (**57**)-like metabolites	Present only in *M. acridum*.[27]
M-PKS16 (MaPKS2 in *M. anisopliae* E6)	Acyl pyrones such as aurovertin D (**58**) and its congeners	Only present in host generalists.[27] Aurovertins were isolated from *M. anisopliae*[42] and predicted to be the products of MaPKS2.[26, 43]
M-PKS18	Predicted fusarielin A (**59**)-like compounds	Absent only from *M. acridum*.[27]
M-PKS21 (Ma-PKS1 in	Predicted stipitaldehyde-derived acyl-	Present in all sequenced *Metarhizum* spp.[27] Induced in *M. anisopliae*

M. anisopliae E6)	benzaldehydes similar to tropolone (**60**) and stipitatic acid (**61**)[44]	under conditions mimicking early infection.[26]
M-PKS24 (MaTERP-PKS1 in *M. anisopliae* E6; SubA in *M. robertsii* ARSEF 23) + M-TER14 + M-TER33 + M-TER43	Subglutinol A (**25**) and its congeners[30]	Absent only from *M. album*.[27] Subglutinols were isolated from *M. robertsii* as the products of the Sub BGC.[30]
M-PKS27 (MrPKS2 in *M. robertsii*)	Predicted 1,8-dihydroxynaphthalene (**62**)-derived melanin	Absent only from *M. album*.[27] Knockout of MrPKS2 in *M. robertsii* does not alter melanization.[45]
M-PKS28 (MrPKS1 in *M. robertsii*)	Green non-melanin conidial pigment with a putative *nor*-rubrafusarin (**63**)-derived skeleton[45]	Present in all sequenced *Metarhizum* spp.[27] Disruption does not affect virulence.[45]
M-PKS31	Predicted metabolites similar to viridicatumtoxin (**64**)[46]	Present in all sequenced *Metarhizum* spp.[27]
M-PKS32 (MaPKS18 in *M. anisopliae* E6)	Predicted emodin (**65**)-derived anthraquinones[47]	Absent from host specialist *Metarhizium* spp.[27] Induced in *M. anisopliae* under conditions mimicking early infection but repressed under those for late infection.[26]
M-HPN1 (MaNRPS-PKS3 in *M. anisopliae* E6)	Predicted metabolites similar to pyranonigrin B (**66**)[48]	Present in all sequenced *Metarhizum* spp.[27] Repressed in *M. anisopliae* under conditions mimicking early or late infection.[26]

M-HPN2 (NGS1 in *M. robertsii*; MaNRPS-PKS1 in *M. anisopliae* E6)	NG-39x (NG-391 (**67**) and NG-393)[49]	Absent from host specialists.[27] NGS1 was shown to be responsible for NG-39x production in *M. robertsii*. Its deletion does not diminish virulence. Induced in *M. anisopliae* under conditions mimicking early infection and repressed under those for late infection.[26, 49]
M-HPN3	Predicted metabolites similar to deacetylcytochalasin C (**68**)[50]	Present only in *M. guizhouense* and *M. brunneum*.[27] Deacetylcytochalasin C was isolated from *M. anisopliae.*[50]
M-HPN7 (MaNRPS-PKS2 in *M. anisopliae* E6) + M-TER44	Predicted prenylated metabolites similar to pseurotin A (**69**)[51]	Present in host generalist *Metarhizium* spp. only.[27] Induced in *M. anisopliae* during growth conditions mimicking early infection and repressed under those for late infection.[26]
M-IH1 (MaPKS10 in *M. anisopliae* E6; SwnK in *M. robertsii* ARSEF 23)	Swainsonine (**16**)[52]	Missing from *M. album* only.[27] Swainsonine has been isolated from *M. robertsii* as the product of the SWN cluster.[53] Repressed in *M. anisopliae* under conditions mimicking both early and late infection.[26]
M-TER1	Predicted squalene / hopane-type metabolites similar to hopanediol (**70**)[54]	Present only in *M. guizhouense*.[27]
M-TER3 (MaTERP1 in *M. anisopliae* E6)	Fusidane triterpenes such as helvolic acid (**71**)[55, 56]	Absent from host-specialist *Metarhizium* spp.[27] Helvolic acid has been isolated from *M. anisopliae.*[56] Induced in *M. anisopliae* under conditions mimicking early infection but repressed in those for late infection.[26]
M-TER10 + M-TER11 + M-TER24 + M-TER26 + M-TER31	Predicted terpendole E (**72**) / lolitrem-type indole diterpenes	Present in all sequenced *Metarhizium* spp.[27]

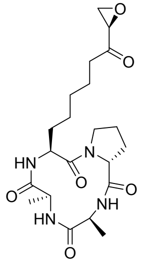
M-TER37	Predicted trichodiene (**73**)-derived metabolites[57]	Absent from *M. album* only.[27]

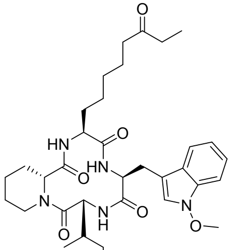
[1] Core gene groups: M-NRPS, *Metarhizium* nonribosomal peptide synthetase; M-NPL, *Metarhizium* NRPS-like enzyme; M-PKS, *Metarhizium* polyketide synthase; M-HPN, *Metarhizium* hybrid PKS-NRPS; M-IH, *Metrhizium* inverted hybrid PKS-NRPS; M-TER, *Metarhizium* terpene biosynthesis-related enzyme.[27] Multiple core enzymes are grouped when they are part of a single putative BGC.

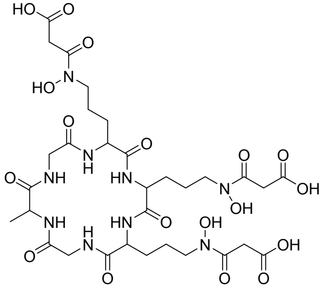
[2] Secondary metabolite products are predicted[26] [27] in most cases based on the orthology of their core genes and the similarity of the BGC gene content to those of known secondary metabolites from other organisms. However, in some cases, the correlation between the BGC and the secondary metabolite has been confirmed by gene disruptions. In yet other cases, the secondary metabolite has been isolated from a *Metarhizium* strain and the BGC is congruent with such a metabolite, but functional identification of the BGC has not been completed. See Figure S1 for structures.

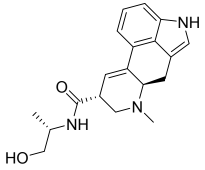
[3] *Metarhizium* genomes considered in these analyses were A) Host specialists: *M. acridum* CQMa 102 and *M. album* ARSEF 1941; B) Metarhizia with an intermediate host range: *M. guizhouense* ARSEF 977 and *M. majus* ARSEF 297; and C) Host generalists: *M. anisopliae* E6; *M. anisopliae* ARSEF 549; *M. brunneum* ARSEF 3297; *M. robertsii* ARSEF 23; and *M. robertsii* ARSEF 2575.[26] [27]

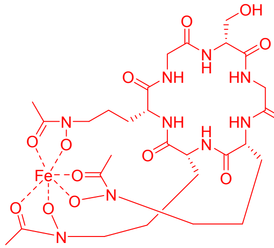
*M-NRPS(PerA), The peramine NRPS was not analyzed by Sbaraini *et al*.[26] or Donzelli *et al*.[27] as this bimodular NRPS was missed in the *M. majus* ARSEF 297 genome sequence,[55] and was identified only after third-party annotation by Berry *et al*.[29]

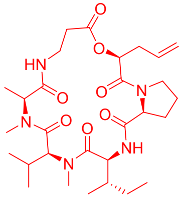

HC-toxin (**44**)

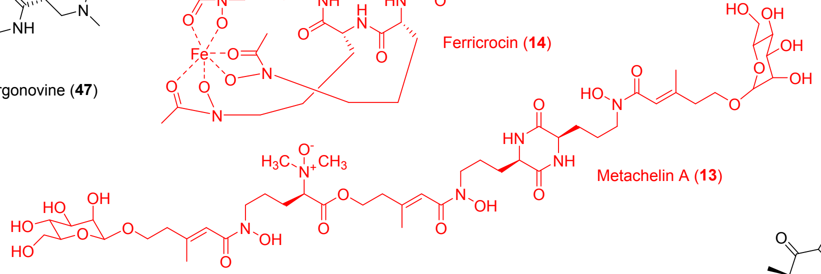

Apicidin (**45**)

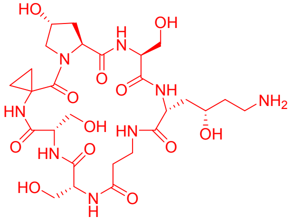

Malonichrome (**46**)

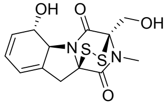

Ergonovine (**47**)

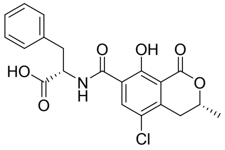

Ferricrocin (**14**)

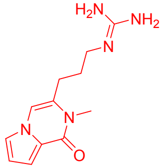

Destruxin A (**48**)

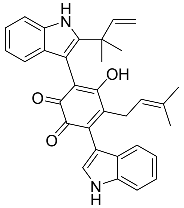

Metachelin A (**13**)

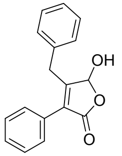

Serinocyclin A (**49**)

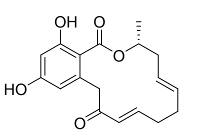

Gliotoxin (**50**)

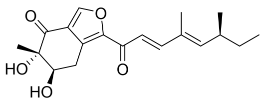

Ochratoxin A (**51**)

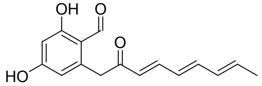

Peramine (**35**)

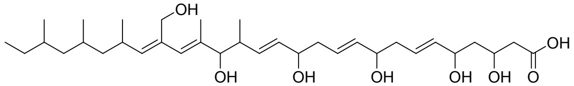

Terrequinone (**52**)

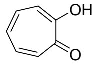

Microperfuranone (**53**)

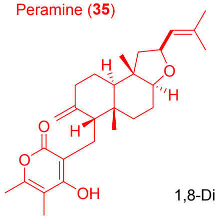

Monocillin II (**54**)

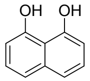

Asperfuranone (**55**)

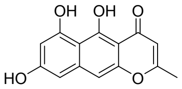

Acyl orsellinaldehyde (**56**)

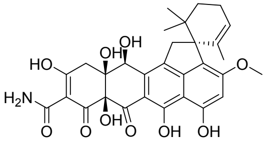

Phomenoic acid (**57**)

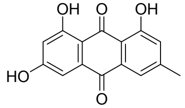

Tropolone (**60**)

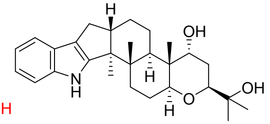

Subglutinol A (**25**)

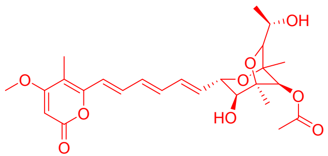

1,8-Dihydroxynaphthalene (**62**)

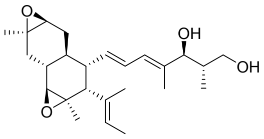

nor-Rubrafusarin (**63**)

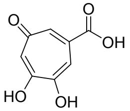

Viridicatumtoxin (**64**)

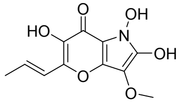

Emodin (**65**)

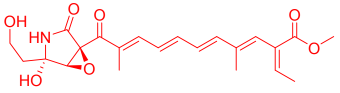

Terpendole E (**72**)

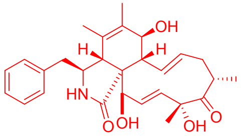

Aurovertin D (**58**)

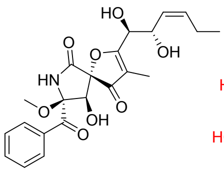

Fusarielin A (**59**)


Stipitatic acid (**61**)


Pyranonigrin B (**66**)


NG-391 (**67**)


Deacetylcytochalasin C (**68**)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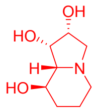
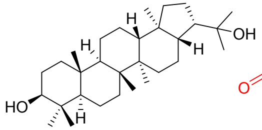
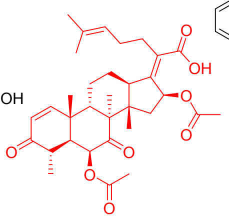

Swainsonine (**16**)


21-βH-Hopane-3β,22-diol (**70**)


Helvolic acid (**71**)

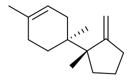

Trichodiene (**73**)

Figure S1. Genomics-based survey of the PK, NRP, PK-NRP hybrid, and terpenoid parvome of *Metarhizium* spp. whose genome sequences have analyzed.[26] [27] [28] [29] [30] PK, NRP, PK-NRP hybrid and terpenoid SMs isolated from metarhizia with completely sequenced genomes are shown in *red*. SMs shown in *black* have been isolated from other fungi and exemplify the predicted metabolites that BGCs with PKS, NRPS, PKS-NRPS hybrid, or terpene synthesis-related core genes encoded in the analyzed *Metarhizium* spp. genomes may produce.[26] [27] [28] [29] [30] Compounds that have been isolated from various *Metarhizium* spp. but have not been correlated with a BGC with a PKS, NRPS, PKS-NRPS hybrid, or terpene synthesis-related core gene from a completely sequenced metarhizial genome are not shown. *Metarhizium* genomes considered in these analyses were A) Host specialists: *M. acridum* CQMa 102 and *M. album* ARSEF 1941; B) Metarhizia with an intermediate host range: *M. guizhouense* ARSEF 977 and *M. majus* ARSEF 297; and C) Host generalists: *M. anisopliae* E6; *M. anisopliae* ARSEF 549; *M. brunneum* ARSEF 3297; *M. robertsii* ARSEF 23; and *M. robertsii* ARSEF 2575.[26] [27] See Table S1 for further descriptions.

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